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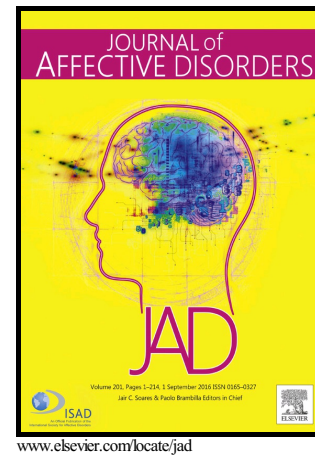
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Empirically Derived Patterns of Psychiatric Symptoms in Youth:
A Latent Profile Analysis

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Abstract

Background: By conceptualizing domains of behavior transdiagnostically, the National Institute of Mental Health Research Domain Criteria (NIMH RDoC) initiative facilitates new ways of studying psychiatric symptoms. In this study, latent profile analysis (LPA) was used to empirically derive classes or patterns of psychiatric symptoms in youth that transect traditional nosologic boundaries.

Methods: Data were drawn from 509 children and adolescents (ages 7 to 18 years; mean age = 12.9 years; 54% male) who were evaluated in the NIMH Emotion and Development Branch and were heterogeneous with respect to presenting diagnoses and symptoms. Youth and/or their parents completed measures of several core symptom dimensions: irritability, anxiety, depression, and attention deficit hyperactivity disorder (ADHD). LPA was used to parse response patterns into distinct classes, based on the levels of, and interrelations among, scores on the different measures.

Results: Five classes emerged: low levels of symptomatology (52% of sample); anxiety and mild depressive symptoms (17%); parent-reported irritability and ADHD (16%); irritability and mixed comorbid symptoms (10%); and high levels of irritability, anxiety, depression, and ADHD (5%). Importantly, these latent classes cut across informants and the clinical conditions for which youth were initially evaluated. Further, the classes characterized by irritability exhibited the poorest overall functioning.

Limitations: These data were cross-sectional. Examination of external validators, including neurobiological correlates and symptom course, is warranted.

Conclusions: Results inform our understanding of the structure of psychiatric symptoms in youth and suggest new ways to operationalize psychopathology and examine it in relation to neurobiology.

Keywords: symptoms; children; comorbidity; transdiagnostic; latent profile analysis

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Transdiagnostic constructs include neural, cognitive, and behavioral domains that transcend current clinical categories. The National Institute of Mental Health Research Domain Criteria (NIMH RDoC) initiative, recognizing limitations in current nosology, supports research on transdiagnostic constructs (Insel et al., 2010; Sanislow et al., 2010). Such work requires the creation of symptom-based dimensions from multiple DSM categories, which can be linked to measures of genetics and psychobiology (Garvey, Avenevoli, & Anderson, 2016). Among youth, irritability and anxiety represent two dimensional, impairing, and correlated traits (e.g., Copeland, Brotman, & Costello, 2015; Cornacchio, Crum, Cox, Pincus, & Comer, 2016; Savage et al., 2015; Stoddard et al., 2014; Stringaris et al., 2012), which may arise from shared biological vulnerabilities (i.e., multifinality, Cicchetti & Rogosch, 1996). Such interdependent relations among symptom dimensions have implications for the RDoC framework, but have yet to be empirically integrated (see Krueger & DeYoung, 2016). Limited research has examined how these symptom dimensions aggregate into classes, which may provide empirically derived alternatives to a priori DSM diagnoses. The current study uses latent profile analysis (LPA) to empirically identify multidimensional patterns or classes of psychiatric symptoms in youth from measures of these traits. The goal is to generate transdiagnostic symptom profiles, which might be examined in future research on neurobiology and genetics.

It is essential to study severe irritability and anxiety in youth in an integrative manner. Irritability refers to a propensity toward anger, including irritable mood, low frustration tolerance and temper outbursts (reviewed in Leibenluft, 2011). High levels of irritability in youth impair functioning (e.g., Copeland, Angold, Costello, & Egger, 2013) and predict later risk for suicidality (Pickles et al., 2010; see meta-analysis of outcomes of pediatric irritability in Vidal-Ribas, Leibenluft, Valdivieso, Brotman, & Stringaris, 2016). Anxiety

refers to the response to threats. Clinically significant anxiety is among the most prevalent pediatric clinical phenotypes (reviewed in Pine & Klein, 2015). Irritability aligns with the RDoC construct of frustrative nonreward (Dickstein, 2015), while anxiety aligns with the potential threat construct (Blackford & Pine, 2012). Although irritability and anxiety are often studied separately, they significantly co-vary in both community and clinical samples of youth (e.g., Cornacchio et al., 2016; Savage et al., 2015; Stoddard et al., 2014). Recent work suggests common biological substrates (Blair, 2010; Savage et al., 2015) and behavioral deficits (Hommer et al., 2014) across irritability and anxiety.

Previous studies have used factor analytic methods to examine the structure of psychopathology in youth (e.g., Burke et al., 2014; Krieger et al., 2013; Lahey et al., 2004, 2008; reviewed in Vidal-Ribas et al., 2016). These models provide insight into the average relations among symptoms or diagnoses within a population. In contrast, person-centered statistical techniques, such as latent class analysis (LCA), utilize individuals as the unit of analysis, with the purpose of identifying relatively homogeneous subgroups. These techniques have the key advantage of providing information about individuals (Goodman, 1974; Hagenaars & McCutcheon, 2002; Lazarsfeld & Henry, 1968). Most LCA studies use diagnostic or other categorical data (e.g., Olino, Klein, Farmer, Seeley, & Lewinsohn, 2012; Vaidyanathan, Patrick, & Iacono, 2011). LPA, in the present study, differs from LCA in its use of dimensional class indicators (i.e., symptom dimensions), making it relevant to RDoC. Classes are derived empirically based on the levels of, and interrelations among, the dimensional indicators.

This study leveraged a large, carefully phenotyped pediatric sample to delineate multidimensional, transdiagnostic symptom profiles. Analyses targeted dimensional measures of irritability, anxiety, depressive, and attention deficit hyperactivity disorder (ADHD) symptoms, which have not been integrated previously using LPA. Symptoms of depression and ADHD were included

because they often co-occur with irritability and anxiety (e.g., Brotman et al., 2006; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003) and, similarly, may share biological mechanisms with irritability and/or anxiety (e.g., Eley & Stevenson, 1999; Savage et al., 2015; Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012). Based on previous research (e.g., Brotman et al., 2006; Cornacchio et al., 2016; Costello et al., 2003; Savage et al., 2015; Stoddard et al., 2014), we hypothesized that the LPA would identify several different multidimensional symptom profiles, including classes of youth characterized by co-occurring irritability and anxiety, co-occurring irritability and ADHD, and co-occurring anxiety and depression, and that classes characterized by the greatest degree of symptom co-occurrence would exhibit the poorest functioning. Further, we hypothesized that the LPA would not conform to traditional diagnostic boundaries, such that the target conditions or diagnoses for which youth were initially evaluated would be distributed across the obtained classes.

Method

Participants

Five hundred and nine children and adolescents between the ages of 7 and 18 years were included in the LPA. Participants completed the symptom measures as part of research in the NIMH Emotion and Development Branch between 2012 and 2015. All procedures were approved by the NIMH Institutional Review Board. Parents gave written informed consent and youth gave written assent. Participants were recruited through advertisements.

Initial diagnostic interviews determined participants' eligibility for various research protocols, recruiting several clinical groups. The clinical groups included: severe mood dysregulation (Leibenluft, 2011; Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003; on which DSM-5 disruptive mood dysregulation disorder subsequently was formulated);¹ anxiety disorder (comprising social anxiety

disorder, generalized anxiety disorder, and/or separation anxiety disorder); ADHD; bipolar I or II disorder; first-degree relative of individual with bipolar I or II disorder and therefore at familial risk for the disorder; and healthy comparison participants with no current or lifetime diagnosis. First-degree relatives of individuals with bipolar disorder could not meet criteria for any bipolar spectrum disorder themselves; other diagnoses were allowed. Master's- and doctoral-level clinicians administered the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) separately to youth and parents to determine diagnoses based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) criteria. Diagnoses were based on best-estimate procedures generated in a consensus conference led by a senior psychiatrist. Exclusion criteria for all groups included: IQ below 70 or the presence of a severely-impairing pervasive developmental disorder, posttraumatic stress disorder, schizophrenia, substance use within the preceding three months, neurological disorder, or unstable medical illness.

Measures

Latent Profile Indicators

Affective Reactivity Index – Child- and Parent-Report (ARI; Stringaris et al., 2012).

The ARI assesses irritability in youth. Items probe both irritable mood (e.g., “easily annoyed by others”) and temper outbursts (e.g., “loses temper easily”) in the preceding six months. A total score (range = 0-12) is determined separately for the Child- and Parent-Report forms by summing six items rated on 3-point Likert scales. The ARI is both valid and reliable (Stringaris et al., 2012) and has been administered across a range of youth with mood and anxiety disorders (Stoddard et al., 2014). In the present sample, internal consistency was high among the items comprising the Child-Report total score (Cronbach's $\alpha = .85$) and Parent-Report total score (α

= .93). The Child- and Parent-Report total scores were correlated with one another ($r = .51$, $p < .001$).

Screen for Child Anxiety Related Disorders – Child- and Parent-Report (SCARED; Birmaher et al., 1999). The SCARED assesses symptoms of several different anxiety disorders in children and adolescents. Items refer to symptoms in the preceding three months and are rated on 3-point Likert scales. Ratings are summed to a total anxiety symptoms score (range = 0-82) and subscale scores corresponding to different diagnoses. For the LPA, we utilized the separate Child- and Parent-Report total scores in order to be consistent with our inclusion of ARI child and parent total scores. The SCARED has been shown to be both valid and reliable (Birmaher et al., 1999). In the current sample, internal consistency was high among the items comprising the Child-Report total score ($\alpha = .95$) and Parent-Report total score ($\alpha = .95$). The Child- and Parent-Report total scores were correlated with one another ($r = .56$, $p < .001$).

Children's Depression Inventory (CDI; Kovacs, 1992). The CDI is a validated measure of self-reported depressive symptoms in youth. Each item presents three different statements referring to thoughts, feelings, and behaviors during the past two weeks; respondents select the statement that best corresponds to their functioning (e.g., "I am sad once in a while"). Responses are scored on 3-point Likert scales and summed to a total score (range = 0-54). Subscale scores also may be computed; however, for the LPA we used the total depressive symptoms score in order to be consistent with the ARI and SCARED total scores. Internal consistency of the CDI was high in the present sample ($\alpha = .91$).

Conners' Parent Rating Scale (CPRS; Conners, 1989). The CPRS measures parent-reported symptoms of childhood ADHD and common comorbidities. Items refer to child functioning during the preceding month and are rated on 4-point Likert scales, which are summed to create various different symptom scales. For the LPA, we utilized raw scores on the total DSM-IV ADHD symptoms

scale (i.e., inattention, hyperactivity, and impulsivity symptoms; range = 0-54) to quantify the overall severity of ADHD symptoms. CPRS raw scores typically are transformed to T-scores as a function of child age and sex; however, we used raw scores in the LPA to be consistent with the ARI, SCARED, and CDI measures. Internal consistency was high among the items comprising the total DSM-IV ADHD symptoms scale ($\alpha = .96$).

Functional Impairment

Children's Global Assessment Scale (CGAS; Shaffer et al., 1983). The CGAS is a single-item, clinician-rated measure of overall child functioning in the past month. Scores range from 1 (lowest functioning) to 100 (highest functioning), and the scale includes behavioral anchors at 10-point increments to aid clinician ratings. The CGAS has good construct validity and test-retest reliability (e.g., Green, Shirk, Hanze, & Wanstrath, 1994).

Procedure

Clinicians trained to achieve acceptable levels of reliability ($\kappa > .75$) completed the K-SADS-PL with participants and their parents in the laboratory. Youth completed the ARI Child-Report, SCARED Child-Report, and CDI, and parents completed the ARI Parent-Report, SCARED Parent-Report, and CPRS. The timing of administration of the symptom measures relative to the diagnostic interview varied across participants. As described below, selection of data for the LPA maximized available cross-sectional data for each participant. Research personnel provided instructions on the measures and answered any questions. Clinicians also completed CGAS ratings.

Data Reduction and Statistical Analysis

Item-level data were drawn for all participants and their parents who completed the ARI (Child- or Parent-Report), SCARED (Child- or Parent-Report), CDI, or CPRS and whose data were available in the NIMH Emotion and Development Branch electronic database (which began in 2012). We selected data based on the largest number, or set, of these six measures that were administered to that participant and parent within a one-month time interval. If a participant had more than one set of measures meeting these criteria, the first set that was completed was selected. In addition, if data for one item on any measure were missing, the score for this item was imputed using the mean item score for that measure. If data for more than one item were missing on any measure, that measure was considered incomplete and excluded from the dataset. Based on these determinations, 328 participants had scores for all six measures, 103 participants had scores for five measures, 45 participants had scores for four measures, and 33 participants had scores for three or fewer measures (total $N = 509$). There were no significant differences between participants who had missing data and those who did not have missing data with respect to age, $p = .82$, or gender distribution, $p = .74$. Healthy comparison participants were more likely to have missing data than were participants with severe mood dysregulation, ADHD, and familial risk for bipolar disorder, all $ps < .005$ (Bonferroni-corrected), and participants with anxiety disorder were more likely to have missing data than were participants with severe mood dysregulation and ADHD, both $ps < .005$ (Bonferroni-corrected). However, the presence of missing data did not significantly impact the assignment of healthy comparison or anxiety disorder participants to the latent classes. There were no significant differences in the distribution of healthy comparison, $p = .47$, or anxiety disorder participants, $p = .20$, by class as a function of whether they had missing data. Importantly, the LPA employed Full Information Maximum Likelihood estimation to include all cases and estimate missing scores. Raw total scores on the measures were transformed to z-scores for the purposes of analysis. Given the wide age range in the sample, to ensure that the obtained symptom

classes were not an artifact of age differences, we partialled the effect of age on total scores and used the resulting residualized z-scores in the LPA.

LPA was conducted using Mplus Version 7.4 (Muthén & Muthén, 1998-2016), first fitting a two-class solution and then fitting successive solutions with additional numbers of classes until the best-fitting solution was determined. Model fit was evaluated using the Akaike Information Criterion (AIC; Akaike, 1987), Bayesian Information Criteria (BIC; Schwartz, 1978), sample-size adjusted BIC (ABIC; Sclove, 1987), entropy, and bootstrapped parametric likelihood ratio test (BLRT; Nylund et al., 2007), which calculates a p-value for improved fit of the current solution relative to the solution with one less class. Consistent with previous LPA research (e.g., Versella, Piccirillo, Potter, Olino, & Heimberg, 2016), model selection also was based on the size of the smallest derived class, as classes constituting less than approximately 5% of the sample may over-fit the data and, thus, be more likely to fail to replicate in independent datasets. It should be noted that the criteria for determining optimal models in LCA/LPA are not fully resolved, and there remain inherent difficulties in deciding between models (Nylund et al., 2007).

Finally, following derivation of the classes, we examined their associations to clinical and demographic variables. Descriptive associations among the classes and participants' clinical categories were used to test the hypothesis that the LPA would cut across traditional diagnostic boundaries. Associations among the classes and the CGAS were used to test the hypothesis that the classes characterized by the greatest symptom co-occurrence would exhibit the poorest functioning. For the CGAS, we utilized data from the closest available date of administration to the symptom measures, with an upper limit of one year (in either direction). Finally, examining the distribution of classes by sex assessed whether sex differences may drive the obtained classes.

Results

Participant Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. As indicated, participants were assigned to clinical groups. In total, the dataset included 65 sibling pairs and five sibling trios.²

In this full sample, receiver operating characteristic (ROC) curves indicated optimal cutoffs of 2 on the ARI Child-Report and 3 on the ARI Parent-Report for differentiating youth with severe mood dysregulation from healthy comparison youth (see Supplementary Results and Supplementary Table 1). Thus, as expected, mean scores of the full sample on the ARI Child- and Parent-Report were slightly above the ROC-based cutoffs and similar to scores previously reported for mixed diagnostic samples (Stringaris et al., 2012; Stoddard et al., 2014). Mean total scores on the SCARED Child- and Parent-Report were below the recommended cutoff for detecting the presence of an anxiety disorder in clinical populations (> 25 ; Birmaher et al., 1999). Similarly, mean total score on the CDI was below the recommended cutoff for detecting the presence of a depressive disorder (> 13 in clinical and > 19 in community samples; Kovacs, 1992; Smucker, Craighead, Craighead, & Green, 1986) samples. Mean T-score on the CPRS DSM-IV ADHD symptoms scale approximated one standard deviation above the normative community mean, but was not considered 'elevated' (> 65 ; Conners, 1989).³ When examining healthy comparison participants only, all mean scores were below the recommended cutoffs (ARI Child-Report: $M = 1.23$; ARI Parent-Report: $M = 0.43$; SCARED Child-Report: $M = 9.89$; SCARED Parent-Report: $M = 4.39$; CDI: $M = 3.41$; CPRS DSM-IV ADHD: $M = 45.02$). When combining the other groups to create a sample of affected and/or high-risk participants, mean scores approached or were above the recommended cutoffs across the measures (ARI Child-Report: $M = 3.47$; ARI Parent-Report: $M = 4.63$; SCARED Child-Report: $M = 21.93$; SCARED Parent-Report: $M = 20.61$; CDI: $M = 9.01$; CPRS DSM-IV ADHD: $M = 65.41$).

Multidimensional Symptom Profiles

For the LPA, the five-class solution had a lower AIC, BIC, and ABIC, and a significant BLRT, relative to the four-class solution (Table 2). Entropy was slightly lower in the five-class solution than in the four-class solution. The proportion of the sample constituting the smallest class was equivalent in the four- and five-class solutions. The six-class solution had a lower AIC, BIC, and ABIC, and a significant BLRT, relative to the five-class solution. However, in the six-class solution, the proportion of the sample constituting the smallest class was 3%, and entropy was further lower than in the five-class solution. Therefore, the five-class solution was selected as representing the best overall model fit.

Figure 1 displays mean scores (z-scores residualized for age) on the symptom measures as a function of class. Table 3 presents the associated raw or T-scores as a function of class. As shown, the largest class ($n = 264$, 51.87% of sample) was characterized by low levels of symptomatology across all measures. Next, three classes were characterized by moderate-to-high symptoms, relative to both the other classes (Figure 1) and to standardized cutoff scores (Table 3). However, these three classes had elevated scores in different domains. One class ($n = 87$, 17.09% of sample) exhibited a moderate elevation in child-reported anxiety, along with mild elevations in parent-reported anxiety and child-reported depressive symptoms. Another class of similar size ($n = 82$, 16.11% of sample) exhibited moderate elevations in parent-reported irritability and parent-reported ADHD. A smaller class ($n = 52$, 10.22% of sample) exhibited high elevations in child- and parent-reported irritability along with mixed comorbid symptoms; the latter included moderate elevations in child- and parent-reported anxiety, a mild elevation in depressive symptoms, and a high elevation in ADHD. The fifth, smallest class ($n = 24$, 4.72% of sample) was characterized by consistently high levels of irritability, anxiety, depressive symptoms, and ADHD, with particularly high child-report measures.

Associations with Clinical Categories

Descriptive associations among the multidimensional symptom classes and participants' designated clinical groups appear in Table 4. As shown, the classes cut across diagnoses for which youth were initially evaluated: each class was distributed across some or all diagnoses, and each diagnosis was distributed across some or all classes. The strongest correspondence between class and diagnosis was the preponderance of healthy comparison participants in the class with low levels of symptomatology. Similarly, youth at familial risk for bipolar disorder, but without a personal history of bipolar disorder, largely fell into this low symptomatology class.⁴ In general, participants with severe mood dysregulation or bipolar disorder were distributed among the three classes involving irritability and co-occurring symptoms. Participants in the anxiety disorder group generally were assigned to the classes entailing anxiety symptoms or low levels of symptoms. Finally, the ADHD group was primarily assigned to the classes entailing low symptoms or parent-reported irritability and ADHD.

Associations with Impairment

One-way analysis of variance (ANOVA) compared CGAS score across classes.⁵ The classes differed significantly in CGAS score, $F(4,331) = 38.99$, $p < .001$. Pairwise comparisons indicated that the class characterized by low levels of symptomatology had a higher CGAS score ($M = 69.54$, $SD = 14.08$) than did all other classes, all $ps < .001$. In turn, the class characterized by anxiety symptoms and mild depressive symptoms had a higher CGAS score ($M = 59.97$, $SD = 14.42$) than did all three classes characterized by irritability and co-occurring symptoms, all $ps < .002$. CGAS score did not differ among the classes characterized by parent-reported irritability and ADHD ($M = 51.95$, $SD = 11.81$), irritability and mixed comorbid symptoms ($M = 47.93$, $SD = 7.70$), and consistently high levels of irritability, anxiety, depressive, and ADHD symptoms ($M = 49.55$, $SD = 10.38$), all $ps > .10$. In sum, the

presence of at least moderate-to-high irritability symptoms, reported by either child or parent, was associated with the poorest overall child functioning.

Associations with Sex

An exploratory chi-squared test found that the classes differed in distribution by participant sex, $\chi^2(4, N = 509) = 21.24$ $p < .001$. Specifically, males were disproportionately more likely than females to be included in the class characterized by parent-reported irritability and ADHD ($n = 62$, 22.55% of males; $n = 20$, 8.55% of females). No other class exhibited disproportionate distribution by sex. Thus, on the whole, sex differences in symptom profiles did not appear to be driving the derived classes. Because we residualized symptom scores for age, we did not examine associations with age.

Discussion

The aim of this study was to identify classes of youth based on multidimensional patterns of psychiatric symptoms. As hypothesized, the LPA identified multidimensional symptom profiles that differed in both the levels of symptoms and degree of co-occurrence among symptoms. These profiles included: low levels of all symptomatology; moderate anxiety and mild depressive symptoms; high parent-reported irritability and ADHD; high irritability, high ADHD, and moderate anxiety; and consistently high levels of irritability, anxiety, depression, and ADHD. No 'pure' classes emerged, exhibiting elevations only one symptom dimension, relative to the class with low levels of all symptoms. Also as hypothesized, the empirically derived symptom classes cut across the target diagnoses for which participants were initially evaluated. In future work it will be important to integrate the interdependent associations among symptom dimensions when studying RDoC constructs. These findings highlight the need to expand the lens of future research from single symptom dimensions to the broader patterns among symptoms within individuals, which may provide

insight into common pathophysiological mechanisms. A multidimensional approach may be particularly important in developmental psychopathology research, given its ability to elucidate shared pathophysiological mechanisms early in life, potentially reducing risk for a range of symptoms later in life.

The three classes characterized by irritability and various comorbid symptoms exhibited the poorest overall functioning. These results are consistent with previous studies in which irritability was associated with significant social and academic impairment, parental burden, and high rates of mental health service use (e.g., Copeland et al., 2013; Copeland, Brotman, & Costello, 2015; Dougherty et al., 2013). However, although the three classes involving irritability did not differ in overall functional impairment, in future investigations it will be critical to validate these classes with biology, treatment, and outcome data. In particular, the classes characterized by irritability could be shown to differ in their neural correlates. For example, two of the three classes exhibited moderate or high anxiety symptoms in addition to irritability. This has implications for pathophysiological research.

Neurobiological formulations postulate that anger and fear are mediated by a common neural circuit that encompasses the amygdala, hypothalamus, and periaqueductal gray and is involved in threat processing (Blair, 2010). Therefore, this particular neural circuit may be implicated in the co-occurrence of irritability and anxiety, whereas other, or additional, circuitry may be involved in the co-occurrence of irritability and ADHD or depression. Here, examining irritability as a single dimension could risk obscuring specific pathophysiological mechanisms that mediate particular co-occurring symptoms (Wiggins et al., 2016).

Our smallest obtained class, which was characterized by high levels of irritability, anxiety, depression, and ADHD symptoms, may be consistent phenotypically with prior research on the Child Behavioral Checklist (CBCL) Dysregulation Profile. That work identified a severely affected pediatric phenotype with co-occurring anxiety, depression, attention problems, and aggression (e.g.,

Althoff, Rettew, Ayer, & Hudziak, 2010; Ayer et al., 2009; Basten et al., 2013). In previous studies including large-scale twin analyses, additive genetic effects have been shown to contribute to this profile (e.g., Althoff, Rettew, Faraone, Boomsma, & Hudziak, 2006; Hudziak, Althoff, Derks, Faraone, & Boomsma, 2005). Thus, the multidimensional pattern of symptoms constituting the Dysregulation Profile may have implications for shared biological mechanisms. In the current study, although we did not find youth at familial risk for bipolar disorder to be overrepresented in the high symptomatology class, the analysis was significantly underpowered. Future large-scale studies may continue to examine genetic contributions to multidimensional symptom patterns.

LPA provides a dimensional measure of the estimated probability of each individual in the sample being allocated to each class in a given model. In future work, we suggest testing the neural correlates of these probability measures, because these measures quantify, in a single metric, individuals' propensity to exhibit multiple interrelated symptoms. In addition, LPA empirically establishes categorical thresholds or cutoffs along dimensional measures in order to determine individuals' class membership. This approach ultimately may be useful in clinical settings in which decision-making is often binary (e.g., which treatment to select).

Recently, authors have proposed other ways to integrate a structural psychopathology framework with neurobiologically-based RDoC research. Karalunas and colleagues (2014) used a community detection algorithm, another person-centered approach, to create subgroups of youth with ADHD based on temperament characteristics. The investigators found that three different temperaments within ADHD, labeled 'mild,' 'surgent' (high positive approach motivation), and 'irritable' (high negative emotionality), were differentially associated with patterns of resting-state functional connectivity. In addition, Bertocci et al. (2014) found that patterns of task-based prefrontal-amygdala functional connectivity were associated with distinct developmental trajectories of manic symptoms as derived through latent class growth analysis. Krueger and DeYoung (2016) described the hierarchical-dimensional

model of psychopathology and its potential relevance to the study of RDoC constructs, citing a recent study with adult participants in which resting state imaging was used to examine the neural correlates of an externalizing symptom dimension and its purported subdimensions (antagonism, disinhibition, and substance abuse) (Abram et al., 2015). Coherence measures within different neural networks were differentially related to antagonism, disinhibition, and substance abuse symptoms. This work demonstrates the utility of investigating the neurobiology of multiple interrelated symptom domains within a single study.

Limitations

Several limitations of this study warrant discussion. First, results of the LPA indicated informant discrepancies, in which youth and their parents differed in reported levels of child irritability and child anxiety. Informant discrepancies are common in child psychopathology research (De Los Reyes & Kazdin, 2005). Given that the CDI and CPRS each were only completed by one informant, informant may serve as a confound in the reports of depressive and ADHD symptoms. Therefore, future studies should employ both child- and parent-report measures of depression and ADHD. Second, these data were cross-sectional. While they included several important domains of child psychopathology, others were excluded (e.g., hypo/manic symptoms, autism spectrum symptoms). In particular, the cross-sectional symptom data did not account for the history of hypo/manic symptoms in youth with bipolar disorder, which may have reduced phenotypic distinctions between these youth and those with severe mood dysregulation, ADHD, and anxiety disorder. One relative advantage of diagnostic formulation is inclusion of information on the temporal course of illness (e.g., a history of mania/hypomania in bipolar disorder). Future work may use techniques such as latent growth curve modeling to examine multidimensional symptom trajectories across childhood and adolescence, which also will be critical in assessing the roles of age and neurodevelopment in symptom patterns over time (Casey, Oliveri, & Insel, 2014). For example,

Findling and colleagues (2013) used latent class growth analysis to identify four distinct trajectories of manic symptoms over the course of two years in a youth sample. Third, there was variability across participants in the amount of time between completion of the diagnostic interview and the symptom measures. Fourth, these data represent a convenience sample referred for research. A relatively large portion of the sample was recruited on the basis of target disorders, resulting in higher rates of symptomatology and comorbidity than in the community. Thus, while the rich, well distributed symptomatology exhibited in this sample enabled a fine-grained examination of dimensional profiles, the distribution of symptom levels here will not generalize to population-based work. Fifth, the sample was relatively wealthy with respect to household income; future studies may examine more socioeconomically diverse samples.

Conclusions

The study of dimensions of brain and behavioral functioning requires the articulation of clinically-relevant phenotypes. In the present study, we found that pediatric symptoms of irritability, anxiety, depression, and ADHD formed several different multidimensional phenotypes. These results resonate with the well-known phenomena of comorbidity and multifinality in developmental psychopathology. Future pathophysiological research must grapple with the interdependent relations among symptoms from a developmental, longitudinal perspective; studying a single symptom dimension could result in false differentiation among RDoC constructs or neglecting the influence of one construct on another. As we highlighted, person-centered statistical techniques such as LPA may provide practical, quantitative tools in charting a way forward. Consideration of multidimensional symptom profiles ultimately will aid in identifying mechanisms of complex, challenging clinical presentations, in order to develop novel interventions for those youth in great need of them.

Accepted manuscript

Footnotes

1. Research examining the prospective phenotype of severe mood dysregulation has indicated that 97% of these youth meet criteria for disruptive mood dysregulation disorder (DMDD) (Deveney et al., 2015; see also Stoddard et al., 2015; Tseng et al., 2016). Thus, we estimate that approximately 122 of the 126 SMD participants in the current analyses would meet DMDD criteria.

2. To ensure that sibling relationships were not driving the obtained classes, we reanalyzed the data using one randomly-selected participant from each sibling pair or trio (434 participants total). The resulting symptom profiles did not differ from those in the original model (see Supplementary Figure 1). Therefore, we retained the original model on the full sample.

3. T-scores for four 18-year-old participants were determined using the 15-to-17-year-old age band.

4. Aside from the low symptomatology class, youth at familial risk for bipolar disorder were not differentially distributed across the other four classes, $\chi^2(3) = 3.65$, $p = .30$.

5. CGAS data were missing for 173 participants. The majority ($n = 121$) were healthy comparison participants who were not administered the CGAS; therefore, the CGAS score for the low symptomatology class represents an underestimate. Additional missing CGAS cases ($n = 36$) were distributed across clinical groups and largely due to constraints at the time of the clinical assessment. Finally, 16 CGAS scores were excluded due to the CGAS and symptom measures being completed more than one year apart.

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Table 1

Demographic and Clinical Characteristics of the Sample

Variable	M (SD) or %
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Age (years)	12.91 (2.69)
Gender (% male)	54.03 %
Race	
Caucasian	68.57 %
African-American	15.32 %
Asian-American	4.52 %
Mixed Race/Other	9.43 %
Unknown	2.16 %
Ethnicity (% Non-Hispanic)	90.18 %
Annual Household Income	
Under \$90,000	19.65 %
Between \$90,000 and \$180,000	32.02 %
Over \$180,000	18.47 %
Not reported	29.86 %
Research Group	
Severe Mood Dysregulation	24.75 %
Anxiety Disorder	17.88 %
Attention Deficit Hyperactivity Disorder	12.38 %
Bipolar I or II	5.30 %
At Familial Risk for Bipolar I or II	11.59 %
Healthy Comparison	28.09 %
Symptom Measure Score	
ARI Child (raw score)	2.91 (2.83)
ARI Parent (raw score)	3.57 (3.78)
SCARED Child (raw score)	18.48 (14.58)
SCARED Parent (raw score)	16.15 (14.35)
CDI Child (raw score)	7.43 (7.46)

CPRS DSM-IV ADHD Parent (T-score) 61.04 (15.05)

Note. ARI = Affective Reactivity Index; SCARED = Screen for Child Anxiety Related Disorders; CDI = Children's Depression Inventory; CPRS = Conners' Parent Rating Scale; ADHD = attention deficit hyperactivity disorder. Table 2

Fit Information for Latent Profile Analysis Models with 2-6 Classes

Classes	Free Parameters	Log Likelihood	AIC	BIC	ABIC	Entropy	BLRT	Smallest Class Proportion
2	19	-3587.81	7213.62	7294.04	7233.73	.82	< .001	26%
3	26	-3426.65	6905.31	7015.35	6932.82	.85	< .001	6%
4	33	-3316.07	6698.13	6837.80	6733.06	.87	< .001	5%
5	40	-3278.22	6636.45	6805.75	6678.78	.85	< .001	5%
6	47	-3239.97	6573.94	6772.87	6623.68	.84	< .001	3%

Note. AIC = Akaike Information Criterion; BIC = Bayesian Information Criteria; ABIC = Sample-adjusted BIC; BLRT = bootstrapped parametric likelihood ratio test.

Table 3

Raw Scores on Symptom Measures for Each Class in the Five-Class Solution

Symptom Measure M (SD)	Low Levels of all Symptomatology (n = 264)	Moderate Anxiety and Mild Depressive Symptoms (n = 87)	High Parent- Reported Irritability and ADHD (n = 82)	High Irritability and Mixed Comorbid Symptoms (n = 52)	High Levels of all Symptomatology (n = 24)
ARI Child	1.38 (1.84) ^a	2.97 (2.16) ^b	3.28 (2.00) ^b	6.69 (2.44) ^c	7.70 (2.10) ^d
ARI Parent	1.09 (1.58) ^a	2.18 (2.23) ^b	7.95 (2.34) ^d	8.76 (1.83) ^e	6.90 (4.01) ^c
SCARED Child	10.61 (7.63) ^a	33.65 (9.81) ^d	13.39 (7.73) ^b	25.10 (9.05) ^c	55.72 (8.63) ^e
SCARED Parent	9.23 (10.71) ^a	22.76 (13.42) ^b	19.67 (12.39) ^b	23.60 (13.75) ^b	40.36 (11.02) ^c
CDI Child	3.13 (2.91) ^a	12.69 (5.00) ^c	5.64 (3.70) ^b	13.98 (4.64) ^c	27.96 (7.94) ^d
CPRS DSM-IV ADHD Parent [*]	52.21 (11.66) ^a	59.94 (12.56) ^b	71.68 (9.56) ^c	77.62 (9.88) ^d	70.05 (16.85) ^c

Note. ARI = Affective Reactivity Index; SCARED = Screen for Child Anxiety Related Disorders; CDI = Children's Depression Inventory; CPRS = Conners' Parent Rating Scale; ADHD = attention deficit hyperactivity disorder. ^{*} T-scores. ^{a,b,c,d,e} Different superscripts within rows indicate significant pairwise comparisons between classes, $p < .05$.

Table 4

Class Membership as a Function of Research Group

Research Group	Low Levels of all Symptomatology (n = 264)	Moderate Anxiety and Mild Depressive Symptoms (n = 87)	High Parent- Reported Irritability and ADHD (n = 82)	High Irritability and Mixed Comorbid Symptoms (n = 52)	High Levels of all Symptomatology (n = 24)
Severe Mood Dysregulation (n = 126)	n = 13 10% 5%	n = 18 14% 21%	n = 51 41% 62%	n = 31 25% 60%	n = 13 10% 54%
Anxiety Disorder (n = 91)	n = 42 46% 16%	n = 32 35% 37%	n = 7 8% 9%	n = 6 7% 12%	n = 4 4% 17%
Attention Deficit Hyperactivity Disorder (n = 63)	n = 34 54% 13%	n = 12 19% 14%	n = 12 19% 15%	n = 5 8% 10%	n = 0 0% 0%
Bipolar I or II (n = 27)	n = 4 15% 2%	n = 4 15% 5%	n = 7 26% 9%	n = 8 30% 15%	n = 4 15% 17%
At Familial Risk for Bipolar I or II (n = 59)	n = 39 66% 15%	n = 10 17% 11%	n = 5 9% 6%	n = 2 3% 4%	n = 3 5% 13%
Healthy Comparison (n = 143)	n = 132 92% 50%	n = 11 8% 13%	n = 0 0% 0%	n = 0 0% 0%	n = 0 0% 0%

Note. Percentages on the left side of each column correspond to the proportions of participants in each research group who were allocated to each class, and sum to 100% (approximately, due to rounding) in each row. Percentages on the right side of each column correspond to the proportions of participants in each class who were allocated to each research group, and sum to 100% (approximately, due to rounding) in each column.

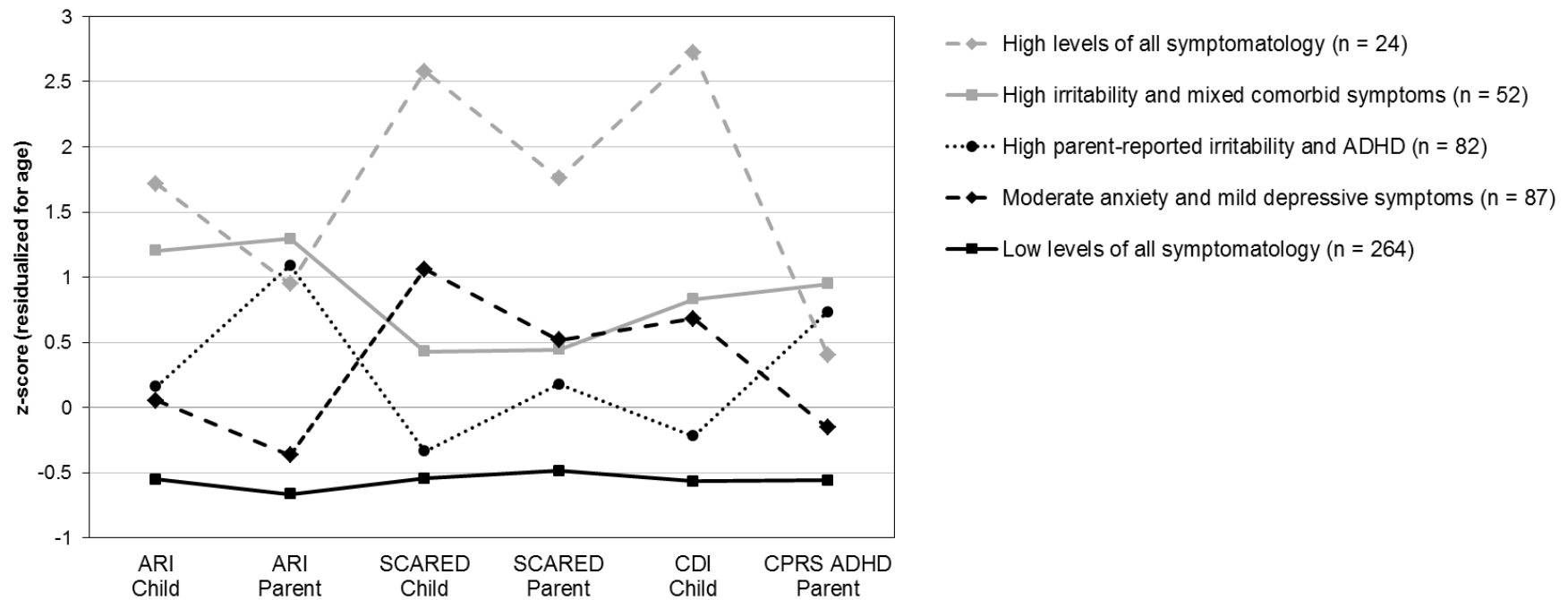


Figure 1. Mean scores on the symptom measures for each class in the five-class solution. Note. ARI = Affective Reactivity Index; SCARED = Screen for Child Anxiety Related Disorders; CDI = Children's Depression Inventory; CPRS = Conners' Parent Rating Scale; ADHD = attention deficit hyperactivity disorder. Class sizes are based on participants' most likely class membership as derived from the five-class solution. Z-scores of 0 should be interpreted separately for each symptom measure in the context of its overall mean in the full sample (Table 1).

Highlights

- The NIMH RDoC initiative supports research on transdiagnostic constructs
- Pediatric symptoms of irritability, anxiety, depression, and ADHD often co-occur
- This study examined how these symptom dimensions aggregate into classes
- Five multidimensional symptom classes emerged, which transected diagnostic categories
- Results suggest new ways to operationalize developmental psychopathology in relation to neurobiology